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| <p>(54) Title: <b>PHENYLALANINE DERIVATIVES AS INTEGRIN INHIBITORS</b></p> <div style="text-align: center; margin: 20px 0;"> <p style="text-align: right;">(1)</p> </div> <p>(57) Abstract</p> <p>Phenylalanine derivatives of formula (1) are described, wherein L<sup>1</sup> is a linker atom or group; X<sup>1</sup> is a group selected from -N(R<sup>3</sup>)CO-, -N(R<sup>3</sup>)SO<sub>2</sub>-, -N(R<sup>3</sup>)C(O)O- or -N(R<sup>3</sup>)CON(R<sup>3a</sup>)-; and R is a carboxylic acid or a derivative thereof. The compounds are able to inhibit the binding of α4 integrins to their ligands and are of use in the prophylaxis and treatment of diseases or disorders involving inflammation.</p>  |                  |   |

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## PHENYLALANINE DERIVATIVES AS INTEGRIN INHIBITORS

5 This invention relates to a series of phenylalanine derivatives, to compositions containing them, to processes for their preparation, and to their use in medicine.

10 Over the last few years it has become increasingly clear that the physical interaction of inflammatory leukocytes with each other and other cells of the body plays an important role in regulating immune and inflammatory responses [Springer, T. A. *Nature*, 346, 425, (1990); Springer, T. A. *Cell* 76, 301, (1994)]. Many of these interactions are mediated by specific cell surface molecules collectively referred to as cell adhesion molecules.

15 The adhesion molecules have been sub-divided into different groups on the basis of their structure. One family of adhesion molecules which is believed to play a particularly important role in regulating immune and inflammatory responses is the integrin family. This family of cell surface glycoproteins has a typical non-covalently linked heterodimer structure. At  
20 least 14 different integrin alpha chains and 8 different integrin beta chains have been identified [Sonnenberg, A. *Current Topics in Microbiology and Immunology*, 184, 7, (1993)]. The members of the family are typically named according to their heterodimer composition although trivial nomenclature is widespread in this field. Thus the integrin termed  $\alpha_4\beta_1$   
25 consists of the integrin alpha 4 chain associated with the integrin beta 1 chain, but is also widely referred to as Very Late Antigen 4 or VLA4. Not all of the potential pairings of integrin alpha and beta chains have yet been observed in nature and the integrin family has been subdivided into a number of subgroups based on the pairings that have been recognised  
30 [Sonnenberg, A. *ibid*].

The importance of cell adhesion molecules in human leukocyte function has been further highlighted by a genetic deficiency disease called Leukocyte Adhesion Deficiency (LAD) in which one of the families of  
35 leukocyte integrins is not expressed [Marlin, S. D. *et al* *J. Exp. Med.* 164, 855 (1986)]. Patients with this disease have a reduced ability to recruit

leukocytes to inflammatory sites and suffer recurrent infections which in extreme cases may be fatal.

5 The potential to modify adhesion molecule function in such a way as to beneficially modulate immune and inflammatory responses has been extensively investigated in animal models using specific monoclonal antibodies that block various functions of these molecules [e.g. Issekutz, T. B. J. Immunol. 3394, (1992); Li, Z. *et al* Am. J. Physiol. 263, L723, (1992); Binns, R. M. *et al* J. Immunol. 157, 4094, (1996)]. A number of  
10 monoclonal antibodies which block adhesion molecule function are currently being investigated for their therapeutic potential in human disease.

One particular integrin subgroup of interest involves the  $\alpha_4$  chain which  
15 can pair with two different beta chains  $\beta_1$  and  $\beta_7$  [Sonnenberg, A. *ibid*]. The  $\alpha_4\beta_1$  pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes and eosinophils) although it is absent or only present at low levels on circulating neutrophils.  $\alpha_4\beta_1$  binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1)  
20 frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L. Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least three sites in the matrix molecule fibronectin [Humphries, M. J. *et al*. Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed  
25 that the interaction between  $\alpha_4\beta_1$  and ligands on other cells and the extracellular matrix plays an important role in leukocyte migration and activation [Yednock, T. A. *et al*, Nature, 356, 63, (1992); Podolsky, D. K. *et al*. J. Clin. Invest. 92, 373, (1993); Abraham, W. M. *et al*. J. Clin. Invest. 93, 776, (1994)].

30 The integrin generated by the pairing of  $\alpha_4$  and  $\beta_7$  has been termed LPAM-1 [Holzmann, B and Weissman, I. EMBO J. 8, 1735, (1989)] and like  $\alpha_4\beta_1$ , binds to VCAM-1 and fibronectin. In addition,  $\alpha_4\beta_7$  binds to an adhesion molecule believed to be involved in the homing of leukocytes to  
35 mucosal tissue termed MAdCAM-1 [Berlin, C. *et al*, Cell, 74, 185, (1993)]. The interaction between  $\alpha_4\beta_7$  and MAdCAM-1 may also be important at

sites of inflammation outside of mucosal tissue [Yang, X-D. *et al*, PNAS, 91, 12604 (1994)].

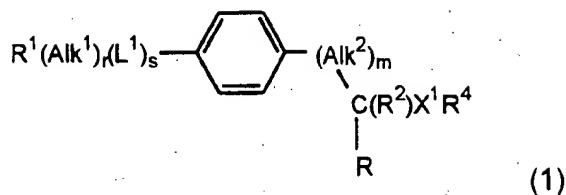
Regions of the peptide sequence recognised by  $\alpha_4\beta_1$  and  $\alpha_4\beta_7$  when they  
5 bind to their ligands have been identified.  $\alpha_4\beta_1$  seems to recognise LDV,  
IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in  
VCAM-1 [Humphries, M. J. *et al*, *ibid*] whilst  $\alpha_4\beta_7$  recognises a LDT  
sequence in MAdCAM-1 [Briskin, M. J. *et al*, J. Immunol. 156, 719,  
(1996)]. There have been several reports of inhibitors of these interactions  
10 being designed from modifications of these short peptide sequences  
[Cardarelli, P. M. *et al* J. Biol. Chem. 269, 18668, (1994); Shroff, H. N.  
Bioorganic. Med. Chem. Lett. 6, 2495, (1996); Vanderslice, P. J. Immunol.  
158, 1710, (1997)]. It has also been reported that a short peptide  
sequence derived from the  $\alpha_4\beta_1$  binding site in fibronectin can inhibit a  
15 contact hypersensitivity reaction in a trinitrochlorobenzene sensitised  
mouse [Ferguson, T. A. *et al*, PNAS 88, 8072, (1991)].

Since the alpha 4 subgroup of integrins are predominantly expressed on  
leukocytes inhibition of their ligand binding functions can be expected to be  
20 beneficial in a number of immune or inflammatory disease states.  
However, because of the ubiquitous distribution and wide range of  
functions performed by other members of the integrin family it is very  
important to be able to identify selective inhibitors of the alpha 4 subgroup.

25 We have now found a group of compounds which are potent and selective  
inhibitors of the binding of  $\alpha_4$  integrins to their ligands. Members of the  
group are able to inhibit the binding of  $\alpha_4$  integrins such as  $\alpha_4\beta_1$  and/or  
 $\alpha_4\beta_7$  to their ligands at concentrations at which they generally have no or  
minimal inhibitory action on  $\alpha$  integrins of other subgroups. The  
30 compounds are thus of use in medicine, for example in the prophylaxis  
and treatment of immune or inflammatory disorders as described  
hereinafter.

Thus according to one aspect of the invention we provide a compound of  
35 formula (1)

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wherein

R is a carboxylic acid (CO<sub>2</sub>H) or a derivative thereof;

5 R<sup>1</sup> is a hydrogen atom or a hydroxyl, straight or branched alkoxy or optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Alk<sup>1</sup> is an optionally substituted aliphatic or heteroaliphatic chain;

L<sup>1</sup> is a linker atom or group;

10 r and s, which may be the same or different, is each zero or an integer 1 provided that when r is zero R<sup>1</sup> is an optionally substituted cycloaliphatic, polycycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Alk<sup>2</sup> is a straight or branched alkylene chain;

m is zero or an integer 1;

15 R<sup>2</sup> is a hydrogen atom or a methyl group;

X<sup>1</sup> is a group selected from -N(R<sup>3</sup>)CO- (where R<sup>3</sup> is a hydrogen atom or a straight or branched alkyl group); -N(R<sup>3</sup>)SO<sub>2</sub>-, -N(R<sup>3</sup>)C(O)O- or -N(R<sup>3</sup>)CON(R<sup>3a</sup>)- (where R<sup>3a</sup> is a hydrogen atom or a straight or branched alkyl group);

20 R<sup>4</sup> is an optionally substituted aliphatic, cycloaliphatic or polycycloaliphatic group;

and the salts, solvates, hydrates and N-oxides thereof, for use in modulating cell adhesion.

25 The compounds of formula (1) are potent and selective inhibitors of the binding of α<sub>4</sub> integrins to their ligands. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter. In particular compounds of the invention are advantageously selective α<sub>4</sub>β<sub>1</sub> inhibitors

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The compounds of formula (1) are thus of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or

disorders involving inflammation in which the extravasation of leukocytes plays a role. The invention extends to such a use and to the use of compounds of formula (1) for the manufacture of a medicament for treating such diseases or disorders. Diseases or disorders of this type include  
5 inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

10 For the prophylaxis or treatment of disease the compounds of formula (1) may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents, for use in  
15 modulating cell adhesion, particularly in the prophylaxis and treatment of diseases or disorders involving inflammation as just described.

Pharmaceutical compositions for use according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal  
20 administration, or a form suitable for administration by inhalation or insufflation and the invention extends to the use of a compound of formula (1) in the manufacture of such formulations.

For oral administration, the pharmaceutical compositions may take the  
25 form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium  
30 glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution  
35 with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable

additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

- 5 Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

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The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection

- 15 may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle; e.g. sterile pyrogen-free water, before use.

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In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

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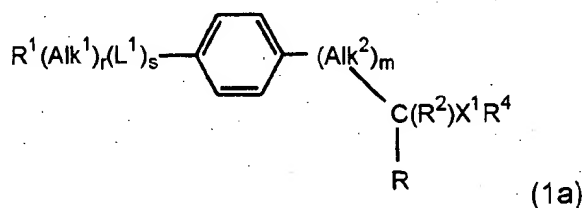
For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichloro-  
30 fluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

- The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the  
35 active ingredient. The pack or dispensing device may be accompanied by instructions for administration.



The quantity of a compound of formula (1) required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, effective daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

Particular compounds of formula (1) form a further feature of the invention and in a further aspect we therefore provide a compound of formula (1a):



wherein

R is a carboxylic acid (-CO<sub>2</sub>H) or a derivative thereof;

R<sup>1</sup> is an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Alk<sup>1</sup> is an optionally substituted aliphatic or heteroaliphatic chain;

L<sup>1</sup> is a linker atom or group;

r and s, which may be the same or different, is each zero or an integer 1;

Alk<sup>2</sup> is a straight or branched alkylene chain;

m is zero or an integer 1;

R<sup>2</sup> is a hydrogen atom or a methyl group;

X<sup>1</sup> is a group selected from -N(R<sup>3</sup>)CO- (where R<sup>3</sup> is a hydrogen atom or a straight or branched alkyl group); -N(R<sup>3</sup>)SO<sub>2</sub>-, -N(R<sup>3</sup>)C(O)O- or -N(R<sup>3</sup>)CON(R<sup>3a</sup>)- (where R<sup>3a</sup> is a hydrogen atom or a straight or branched alkyl group);

R<sup>4</sup> is an optionally substituted aliphatic, cycloaliphatic or polycycloaliphatic group;

and the salts, solvates, hydrates and N-oxides thereof.

- 5 It will be appreciated that compounds of formulae (1) and (1a) may have one or more chiral centres. Where one or more chiral centres is present, enantiomers or diastereomers may exist, and the invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formulae (1) and (1a) and the formulae  
10 hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise.

- In the compounds of formulae (1) and (1a), derivatives of the carboxylic acid group R include carboxylic acid esters and amides. Particular esters  
15 and amides include those -CO<sub>2</sub>R<sup>5a</sup> and -CON(R<sup>5a</sup>)<sub>2</sub> groups described below.

- When in the compounds of formulae (1) and (1a) L<sup>1</sup> is present as a linker atom or group it may be any divalent linking atom or group. Particular  
20 examples include -O- or -S- atoms or -C(O)-, -C(O)O-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, -N(R<sup>5</sup>)- [where R<sup>5</sup> is a hydrogen atom or a straight or branched alkyl group], -CON(R<sup>5</sup>)-, -OC(O)N(R<sup>5</sup>)-, -CSN(R<sup>5</sup>)-, -N(R<sup>5</sup>)CO-, -N(R<sup>5</sup>)C(O)O-, -N(R<sup>5</sup>)CS-, -S(O)N(R<sup>5</sup>)-, -S(O)<sub>2</sub>N(R<sup>5</sup>)-, -N(R<sup>5</sup>)S(O)-, -N(R<sup>5</sup>)S(O)<sub>2</sub>-, -N(R<sup>5</sup>)CON(R<sup>5</sup>)-, -N(R<sup>5</sup>)CSN(R<sup>5</sup>)-, -N(R<sup>5</sup>)SON(R<sup>5</sup>)- or  
25 -N(R<sup>5</sup>)SO<sub>2</sub>N(R<sup>5</sup>)- groups. Where the linker group contains two R<sup>5</sup> substituents, these may be the same or different.

- Alk<sup>2</sup> in the compounds of formulae (1) and (1a) may be for example a straight or branched C<sub>1-3</sub>alkylene chain. Particular examples include  
30 -CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>- and -(CH<sub>2</sub>)<sub>2</sub>-.

When R<sup>3</sup>, R<sup>3a</sup> and/or R<sup>5</sup> in the compounds of formula (1) is a straight or branched alkyl group it may be a straight or branched C<sub>1-6</sub> alkyl group, e.g. a C<sub>1-3</sub> alkyl group such as a methyl or ethyl group.

When Alk<sup>1</sup> in compounds of formula (1) is an optionally substituted aliphatic chain it may be an optionally substituted C<sub>1-10</sub> aliphatic chain. Particular examples include optionally substituted straight or branched C<sub>1-6</sub> alkylene, C<sub>2-6</sub> alkenylene, or C<sub>2-6</sub> alkynylene chains.

5

Heteroaliphatic chains represented by Alk<sup>1</sup> include the aliphatic chains just described but with each chain additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L<sup>2</sup> where L<sup>2</sup> is as defined above for L<sup>1</sup> when L<sup>1</sup> is a linker atom or group. Each L<sup>2</sup> atom or group may interrupt the aliphatic chain, or may be positioned at its terminal carbon atom to connect the chain to the atom or group R<sup>1</sup>.

10

Particular examples of aliphatic chains represented by Alk<sup>1</sup> include optionally substituted -CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>-, -CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>-, -C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>3</sub>CH<sub>2</sub>-, -CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>-, -C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>4</sub>CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>5</sub>CH<sub>2</sub>-, -CHCH-, -CHCHCH<sub>2</sub>-, -CH<sub>2</sub>CHCH-, -CHCHCH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CHCHCH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>CHCH-, -CC-, -CCCH<sub>2</sub>-, -CH<sub>2</sub>CC-, -CCCH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CCCH<sub>2</sub>-, or -(CH<sub>2</sub>)<sub>2</sub>CC- chains. Where appropriate each of said chains may be optionally interrupted by one or two atoms and/or groups L<sup>2</sup> to form an optionally substituted heteroaliphatic chain. Particular examples include optionally substituted -L<sup>2</sup>CH<sub>2</sub>-, -CH<sub>2</sub>L<sup>2</sup>CH<sub>2</sub>-, -L<sup>2</sup>(CH<sub>2</sub>)<sub>2</sub>-, -CH<sub>2</sub>L<sup>2</sup>(CH<sub>2</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>L<sup>2</sup>CH<sub>2</sub>-, -L<sup>2</sup>(CH<sub>2</sub>)<sub>3</sub>- and -(CH<sub>2</sub>)<sub>2</sub>L<sup>2</sup>(CH<sub>2</sub>)<sub>2</sub>- chains.

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The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk<sup>1</sup> include one, two, three or more substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl, C<sub>1-6</sub>alkoxy, e.g. methoxy or ethoxy, thiol, C<sub>1-6</sub>alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include -NHR<sup>5</sup> and -N(R<sup>5</sup>)<sub>2</sub> groups where R<sup>5</sup> is a straight or branched alkyl group as defined above. Where two R<sup>5</sup> groups are present these may be the same or different. Particular examples of substituted chains represented by Alk<sup>1</sup> include those specific chains just described substituted by one, two, or three halogen atoms such

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as fluorine atoms, for example chains of the type  $-\text{CH}(\text{CF}_3)-$ ,  $-\text{C}(\text{CF}_3)_2-$ ,  $-\text{CH}_2\text{CH}(\text{CF}_3)-$ ,  $-\text{CH}_2\text{C}(\text{CF}_3)_2-$ ,  $-\text{CH}(\text{CF}_3)-$  and  $-\text{C}(\text{CF}_3)_2\text{CH}_2$ .

Alkoxy groups represented by  $\text{R}^1$  in compounds of formula (1) include  
5 straight or branched  $\text{C}_{1-6}$  alkoxy groups such as methoxy and ethoxy groups.

When  $\text{R}^1$  is present in compounds of formulae (1) and (1a) as an optionally substituted cycloaliphatic group it may be an optionally  
10 substituted  $\text{C}_{3-10}$  cycloaliphatic group. Particular examples include optionally substituted  $\text{C}_{3-10}$  cycloalkyl, e.g.  $\text{C}_{3-7}$  cycloalkyl, or  $\text{C}_{3-10}$  cycloalkenyl e.g.  $\text{C}_{3-7}$  cycloalkenyl groups.

Optionally substituted heterocycloaliphatic groups represented by  $\text{R}^1$   
15 include the optionally substituted cycloaliphatic groups just described for  $\text{R}^1$  but with each group additionally containing one, two, three or four heteroatoms or heteroatom-containing groups  $\text{L}^2$  as just defined.

Optionally substituted polycycloaliphatic groups represented by  $\text{R}^1$  include  
20 optionally substituted  $\text{C}_{7-10}$  bi- or tricycloalkyl or  $\text{C}_{7-10}$  bi- or tricycloalkenyl groups. Optionally substituted polyheterocycloaliphatic groups represented by  $\text{R}^1$  include the optionally substituted polycycloalkyl groups just described, but with each group additionally containing one, two, three or four  $\text{L}^2$  atoms or groups.

25 Particular examples of  $\text{R}^1$  cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and polyheterocycloaliphatic groups include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolynyl, e.g. 2-imidazolynyl, imidazolidinyl, pyrazolynyl, e.g. 2-pyrazolynyl, pyrazolidinyl, thiazolynyl, thiazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, piperidinone, 1,4-dioxanyl, morpholynyl, morpholinone,  
30 1,4-dithianyl, thiomorpholynyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl,

isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or oxadiazinyl e.g. 1,3,5-oxadiazinyl groups.

The optional substituents which may be present on the R<sup>1</sup> cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or polyheterocycloaliphatic groups include one, two, three or more substituents represented by R<sup>6</sup>, each R<sup>6</sup> substituent being selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C<sub>1-6</sub>alkyl, e.g. methyl or ethyl, haloC<sub>1-6</sub>alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. -C(OH)(CF<sub>3</sub>)<sub>2</sub>, C<sub>1-6</sub>alkoxy, e.g. methoxy or ethoxy, haloC<sub>1-6</sub>alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C<sub>1-6</sub>alkylthio e.g. methylthio or ethylthio, or -(Alk)<sub>v</sub>R<sup>7</sup> groups in which Alk is a straight or branched C<sub>1-3</sub>alkylene chain, v is zero or an integer 1 and R<sup>7</sup> is a -OH, -SH, -N(R<sup>5a</sup>)<sub>2</sub>, -CN, -CO<sub>2</sub>R<sup>5a</sup>, -NO<sub>2</sub>, -CON(R<sup>5a</sup>)<sub>2</sub>, -CSN(R<sup>5a</sup>)<sub>2</sub>, -COR<sup>5a</sup>, -CSN(R<sup>5a</sup>)<sub>2</sub>, -N(R<sup>5a</sup>)COR<sup>5a</sup>, -N(R<sup>5a</sup>)CSR<sup>5a</sup>, -SO<sub>2</sub>N(R<sup>5a</sup>)<sub>2</sub>, -N(R<sup>5a</sup>)SO<sub>2</sub>R<sup>5a</sup>, -N(R<sup>5a</sup>)CON(R<sup>5a</sup>)<sub>2</sub>, -N(R<sup>5a</sup>)CSN(R<sup>5a</sup>) or -N(R<sup>5a</sup>)SO<sub>2</sub>N(R<sup>5a</sup>)<sub>2</sub> group in which R<sup>5a</sup> is an atom or group as defined herein for R<sup>5</sup>.

In the compounds of formulae (1) and (1a), optionally substituted aromatic groups represented by the group R<sup>1</sup> include for example monocyclic or bicyclic fused ring C<sub>6-12</sub> aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups, optionally substituted by one, two, three or more R<sup>6</sup> atoms or groups as just described for R<sup>1</sup> cycloaliphatic groups.

Optionally substituted heteroaromatic groups, represented by the group R<sup>1</sup> in compounds of formulae (1) and (1a) include for example optionally substituted C<sub>1-9</sub> heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered fused-ring

heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include  
 5 optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-C<sub>1-6</sub>imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]-  
 10 benzofuryl, benzothienyl, benzotriazolyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and imidyl,  
 15 e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Optional substituents which may be present on R<sup>1</sup> heteroaromatic groups include one, two, three or more R<sup>6</sup> atoms or groups as described above  
 20 for R<sup>1</sup> cycloaliphatic groups.

Particular aliphatic groups represented by R<sup>4</sup> in compounds of formulae (1) and (1a) include optionally substituted C<sub>1-10</sub>aliphatic groups. Particular examples include optionally substituted straight or branched C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl or C<sub>2-6</sub>alkynyl groups. Optional substituents include one, two or  
 25 three substituents, where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl, C<sub>1-6</sub>alkoxy, e.g. methoxy or ethoxy, thiol, C<sub>1-6</sub>alkylthio, e.g. methylthio or ethylthio, haloC<sub>1-6</sub>alkoxy, e.g. fluoroC<sub>1-6</sub>alkoxy  
 30 such as difluoromethoxy or trifluoromethoxy, -N(R<sup>5b</sup>)<sub>2</sub> [where R<sup>5b</sup> is as defined above for R<sup>5</sup>], phenyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkenyl, C<sub>3-7</sub>cycloalkoxy or C<sub>3-7</sub>cycloalkenoxy groups.

Particular examples of R<sup>4</sup> aliphatic groups include optionally substituted  
 35 -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -CH(CH<sub>3</sub>)<sub>2</sub>, -C(CH<sub>3</sub>)<sub>3</sub>, -(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -CH(CH<sub>3</sub>)<sub>3</sub>, -(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>,

-CHCH<sub>2</sub>, -CHCHCH<sub>3</sub>, -CH<sub>2</sub>CHCH<sub>2</sub>, -CHCHCH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CHCHCH<sub>3</sub>,  
-(CH<sub>2</sub>)<sub>2</sub>CHCH<sub>2</sub>, -CH<sub>2</sub>CCCH<sub>3</sub> or -(CH<sub>2</sub>)<sub>2</sub>CCH groups.

When the group R<sup>4</sup> in compounds of formula (1) or (1a) is an optionally  
5 substituted cycloaliphatic group it may be for example an optionally  
substituted C<sub>3-10</sub>cycloaliphatic group. Particular examples include  
optionally substituted C<sub>3-10</sub>cycloalkyl, e.g. C<sub>3-7</sub>cycloalkyl, and C<sub>3-10</sub>  
cycloalkenyl, e.g. C<sub>3-7</sub>cycloalkenyl groups. Optional substituents include  
one, two or three substituents, where each substituent may be the same or  
10 different and is selected from halogen atoms, e.g. fluorine, chlorine,  
bromine or iodine atoms, or hydroxyl, C<sub>1-6</sub>alkoxy e.g. methoxy or ethoxy,  
thiol, C<sub>1-6</sub>alkylthio, e.g. methylthio or ethylthio, C<sub>1-6</sub>alkyl, e.g. methyl or  
ethyl, haloC<sub>1-6</sub>alkyl e.g. fluoroC<sub>1-6</sub>alkyl such as difluoromethyl or  
trifluoromethyl, haloC<sub>1-6</sub>alkoxy, e.g. fluoroC<sub>1-6</sub>alkoxy such as  
15 difluoromethoxy or trifluoromethoxy, phenyl or -N(R<sup>5b</sup>)<sub>2</sub> groups.

Particular examples of R<sup>4</sup> cycloaliphatic groups include optionally  
substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-  
cyclobuten-1-yl, 2-cyclopenten-1-yl and 3-cyclopenten-1-yl groups.

20 Optionally substituted polycycloaliphatic groups represented by R<sup>4</sup> in  
compounds of formula (1) or (1a) include optionally substituted C<sub>7-10</sub>bi- or  
tricycloalkyl, e.g. norbornyl or adamantyl, or C<sub>7-10</sub>bi- or tricycloalkenyl, e.g.  
norbornenyl groups. Optional substituents include one, two or three  
25 substituents as described above in relation to cycloaliphatic groups  
represented by R<sup>4</sup>.

The presence of certain substituents in the compounds of formula (1) may  
enable salts of the compounds to be formed. Suitable salts include  
30 pharmaceutically acceptable salts, for example acid addition salts derived  
from inorganic or organic acids, and salts derived from inorganic and  
organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides,  
35 alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or  
isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or

napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

- 5 Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.
- 10 Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

When present, the aliphatic chain represented by  $\text{Alk}^1$  in compounds of  
15 the invention is preferably a  $-\text{CH}_2-$  chain.

$\text{Alk}^2$  in compounds of formulae (1) and (1a) is preferably a  $-\text{CH}_2-$  chain and  $m$  is preferably an integer 1.

20  $\text{R}^2$  in compounds of formulae (1) and (1a) is preferably a hydrogen atom.

$\text{R}^3$  and  $\text{R}^{3a}$  in compounds of formulae (1) and (1a) is each preferably a hydrogen atom.

25 In general in compounds of formulae (1) and (1a)  $-(\text{Alk}^1)_r(\text{L}^1)_s-$  is preferably  $-\text{CH}_2\text{O}-$  or  $-\text{CON}(\text{R}^5)-$ , especially  $-\text{CONH}-$ .

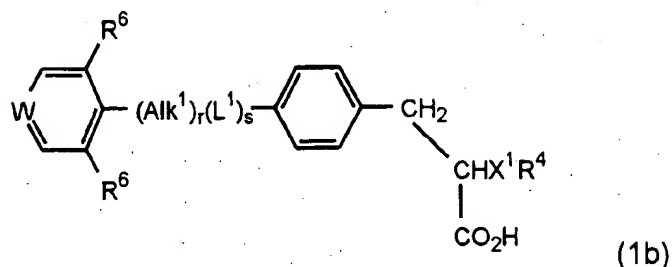
The group  $\text{R}$  in compounds of formulae (1) and (1a) is preferably a carboxylic acid ( $-\text{CO}_2\text{H}$ ) group.

30

In general in compounds of formulae (1) and (1a) the group  $\text{R}^1$  is preferably an optionally substituted aromatic or heteroaromatic group. Particularly useful groups of these types include optionally substituted phenyl, pyridyl or pyrimidinyl groups, particularly those in which the  
35 substituent when present is an atom or group  $\text{R}^6$  as described above.



A particularly useful class of compounds according to the invention has the formula (1b)



wherein -W= is -CH= or -N=, each R<sup>6</sup> group may be the same or different and is as generally defined above, and Alk<sup>1</sup>, r, L<sup>1</sup>, s, X<sup>1</sup> and R<sup>4</sup> are as generally defined above, and the salts, solvates, hydrates and N-oxides thereof.

In compounds of formula (1b) -(Alk<sup>1</sup>)<sub>r</sub>(L<sup>1</sup>)<sub>s</sub>- is preferably a -CH<sub>2</sub>O or -CON(R<sup>5</sup>)- group, especially a -CONH- group.

R<sup>4</sup> in compounds according to formulae (1), (1a) and (1b) is preferably an optionally substituted straight or branched C<sub>1-6</sub>alkyl group or an optionally substituted C<sub>3-7</sub>cycloalkyl or C<sub>7-10</sub>tricycloalkyl group. Particular examples of such groups include optionally substituted straight or branched C<sub>1-4</sub>alkyl groups as more particularly defined above in relation to compounds of formula (1a), and optionally substituted cyclopropyl, cyclobutyl, cyclopentyl and adamantyl groups.

In one class of compounds according to formula (1), (1a) or (1b) X<sup>1</sup> is present as a -N(R<sup>3</sup>)CO- group where R<sup>3</sup> is a hydrogen atom or a straight or branched alkyl group. In compounds of this type R<sup>4</sup> may for example be an optionally substituted aliphatic or cycloaliphatic group. In general compounds in which X<sup>1</sup> is a -NHCO- group are particularly useful.

Particularly useful compounds according to the invention include:

*N*-Isopropaloyl-*N*-(3,5-dichloroisonicotinoyl)-*L*-4-aminophenylalanine;

*N*-Cyclopropaloyl-*N*-(3,5-dichloroisonicotinoyl)-*L*-4-aminophenylalanine;

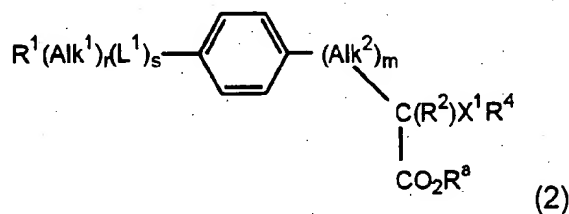
*N*-Acetyl-*N*-(3,5-dichloroisonicotinoyl)-*L*-4-aminophenylalanine;

*N*-(Trimethylacetyl)-*N'*-(2,6-difluorobenzoyl)-*L*-4-aminophenylalanine;  
*N*-(1-Adamantylcarbonyl)-*N'*-(2,6-dichlorobenzoyl)-*L*-4-aminophenyl  
 alanine;  
 and the salts, solvates, hydrates and N-oxides thereof.

5

The compounds of formulae (1) and (1a) may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols  $R^1$ - $R^4$ ,  $L^1$ ,  $Alk^1$ ,  $Alk^2$ ,  $X^1$ ,  $m$ ,  $r$ ,  $s$  and  $R$  when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of the desired compound and the processes described hereinafter are to be understood to extend to such removal of protecting groups. For convenience, the processes described below all refer to the preparation of a compound of formula (1) but clearly the description applies equally to the preparation of compounds of formula (1a).

Thus a compound of formula (1) in which  $R$  is a  $-CO_2H$  group may be obtained by hydrolysis of an ester of formula (2):



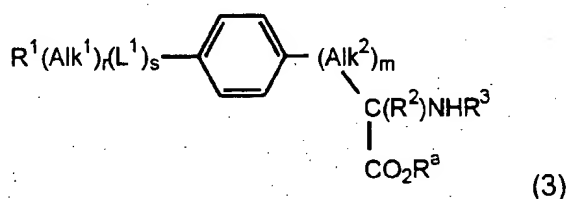
where  $R^a$  is an alkyl group.

30

The hydrolysis may be performed using either an acid or a base depending on the nature of  $R^a$ , for example an organic acid such as

trifluoroacetic acid or an inorganic base such as lithium hydroxide optionally in an aqueous organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol, e.g. methanol at around ambient temperature. Where desired, mixtures of such solvents may be used.

Esters of formula (2) may be prepared by coupling an amine of formula (3):



(where  $\text{R}^a$  is as just described) or a salt thereof with an acid of formula (4):



15

or an active derivative thereof, a chloroformate  $\text{R}^4\text{CO}_2\text{Cl}$ , a sulphonyl halide  $\text{R}^4\text{SO}_2\text{Hal}$  (where Hal is a halogen atom such as a chlorine atom) or an isocyanate  $\text{R}^4\text{NCO}$ .

20

Active derivatives of acids of formula (4) include anhydrides, esters and halides. Particular esters include pentafluorophenyl or succinyl esters.

25

The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out in a solvent, for example an inert organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran, or a halogenated hydrocarbon, such as dichloromethane, at a low temperature, e.g. around  $-30^\circ\text{C}$  to around ambient temperature, optionally in the presence of a base, e.g. an organic base such as an amine, e.g. triethylamine, pyridine, or dimethylaminopyridine, or a cyclic amine, such as N-methylmorpholine.

30

Where an acid of formula (4) is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a  
 5 N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to reaction with the amine of formula (3).

10 Intermediates of formulae (2), (3) and (4), or compounds of formula (1), may be manipulated to introduce substituents to aromatic or heteroaromatic groups or modify existing substituents in groups of these types. Typically, such manipulation may involve standard substitution approaches employing for example alkylation, arylation, heteroarylation,  
 15 acylation, thioacylation, halogenation, sulphonylation, nitration, formylation or coupling reactions. Alternatively, existing substituents may be modified for example by oxidation, reduction or cleavage reactions. Particular examples of such reactions are given below.

20 Thus in one example, a compound wherein  $R^1(Alk^1)_r(L^1)_s$  is a  $-L^1H$  group may be alkylated, arylated or heteroarylated using a reagent  $R^1(Alk^1)_rX$  in which  $R^1$  is other than a hydrogen atom and X is a leaving atom or group such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoro-  
 25 methylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic  
 30 solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

In another example, a compound where  $R^1(Alk^1)_r(L^1)_s$  is a  $-L^1H$  group is a  
 35 hydrogen atom may be functionalised by acylation or thioacylation, for example by reaction with a reagent  $R^1(Alk^1)_rL^1X$  [wherein  $L^1$  is a  $-C(O)-$ ,

C(S)-, -N(R<sup>4</sup>)C(O)- or N(R<sup>4</sup>)C(S)- group], in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature, or by reaction with R<sup>1</sup>(Alk<sup>1</sup>)<sub>r</sub>CO<sub>2</sub>H or an activated derivative thereof, for example as described above for the preparation of esters of formula (2).

In a further example a compound may be obtained by sulphonylation of a compound where R<sup>1</sup>(Alk<sup>1</sup>)<sub>r</sub>(L<sup>1</sup>)<sub>s</sub> is an -OH group by reaction with a reagent R<sup>1</sup>(Alk<sup>1</sup>)<sub>r</sub>L<sup>1</sup>Hal [in which L<sup>1</sup> is -S(O)- or -SO<sub>2</sub>- and Hal is a halogen atom such as chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

In another example, a compound where R<sup>1</sup>(Alk<sup>1</sup>)<sub>r</sub>(L<sup>1</sup>)<sub>s</sub> is a -L<sup>1</sup>H group, may be coupled with a reagent R<sup>1</sup>OH (where R<sup>1</sup> is other than a hydrogen atom) or R<sup>1</sup>Alk<sup>1</sup>OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate to yield a compound containing a R<sup>1</sup>(Alk<sup>1</sup>)<sub>r</sub>O- group.

In a further example, ester groups -CO<sub>2</sub>R<sup>4</sup> or -CO<sub>2</sub>Alk<sup>4</sup> in compounds of formula (1) may be converted to the corresponding acid [-CO<sub>2</sub>H] by acid- or base-catalysed hydrolysis depending on the nature of the group R<sup>4</sup> or Alk<sup>4</sup>. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxane or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

In a second example, -OR<sup>7</sup> [where R<sup>7</sup> represents an alkyl group such as methyl group] groups in compounds of formula (1) may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent

such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around  $-78^{\circ}\text{C}$ .

Alcohol [-OH] groups may also be obtained by hydrogenation of a  
5 corresponding  $-\text{OCH}_2\text{R}^7$  group (where  $\text{R}^7$  is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [-  
10  $\text{CO}_2\text{Alk}^4$  or  $\text{CO}_2\text{R}^4$ ] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, alcohol -OH groups in compounds of formula (1) may  
15 be converted to a corresponding  $-\text{OR}^3$  group by coupling with a reagent  $\text{R}^7\text{OH}$  in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

20 Aminosulphonylamino [ $-\text{NHSO}_2\text{NH}_2$ ] groups in compounds of formula (1) may be obtained, in another example, by reaction of a corresponding amine [ $-\text{NH}_2$ ] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

25 In a further example amine ( $-\text{NH}_2$ ) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in  
30 the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [ $-\text{NH}_2$ ] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with  
35 hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [-NO<sub>2</sub>] group may be reduced to an amine [-NH<sub>2</sub>], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support  
5 such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

Aromatic halogen substituents in compounds of the invention may be  
10 subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example,  
15 a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

In another example, sulphur atoms in compounds of the invention, for  
example when present in the linker group L<sup>1</sup> may be oxidised to the  
20 corresponding sulfoxide using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

Intermediates of formulae (3) and (4), R<sup>4</sup>CO<sub>2</sub>Cl, R<sup>4</sup>SO<sub>2</sub>Hal, R<sup>4</sup>NCO,  
25 R<sup>1</sup>(Alk<sup>1</sup>)<sub>r</sub>X, R<sup>1</sup>(Alk<sup>1</sup>)<sub>r</sub>L<sup>1</sup>X, R<sup>1</sup>(Alk<sup>1</sup>)<sub>r</sub>CO<sub>2</sub>H, R<sup>1</sup>OH and R<sup>1</sup>Alk<sup>1</sup>OH are either known compounds or may be prepared from known starting materials by use of analogous processes to those used for the preparation of the known compounds and/or by treating known compounds by one or more of the alkylation, acylation and other manipulations described herein.

30

N-oxides of compounds of formula (1) may be prepared for example by  
oxidation of the corresponding nitrogen base using an oxidising agent such  
as hydrogen peroxide in the presence of an acid such as acetic acid, at an  
elevated temperature, for example around 70°C to 80°C, or alternatively  
35 by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

|   |                                    |
|---|------------------------------------|
| EDC - 1-(3-dimethylaminopropyl)3-ethylcarbodiimide; |                                    |
| DMF - dimethylformamide;                            | HOBT - 1-hydroxybenzotriazole;     |
| NMM - N-methylmorpholine;                           | Boc - <u>tert</u> -butoxycarbonyl; |
| DMSO - dimethylsulphoxide;                          | Ar - aryl;                         |
| Et - ethyl;   |                                    |

**INTERMEDIATE 1** used in the following Examples is **N-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester** prepared from 3,5-dichloroisonicotinoyl chloride and N-Boc-L-4-aminophenylalanine methyl ester.



**INTERMEDIATE 2****N-Boc-N'-(2,6-Difluorobenzoyl)-L-4-aminophenylalanine methyl ester**

A mixture of 2,6-difluorobenzoic acid (10g, 63.3mmol) and DMF (3 drops) in dichloromethane (150ml) was treated with thionyl chloride (23ml, 316.5mmol). The mixture was heated at reflux overnight. The solvent was removed *in vacuo* and the residue azeotroped (toluene 3 x 50ml) to give 2,6-difluorobenzoyl chloride as an oil (8.59g, 77%). N-Boc-L-4-aminophenylalanine methyl ester (100.92g, 40.6mmol) and NMM (5.3ml, 48.7mmol) were added to a solution of the above acid chloride in DMF (50ml). The mixture was stirred at room temperature for 2h. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and aqueous. The aqueous layer was extracted with ethyl acetate (3 x 100ml). The combined organic layers were dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to give a pale brown oily solid. Trituration with ether gave the title compound as a white solid (6.93g).  $\delta_H$  (d<sup>6</sup> DMSO) 7.67-7.53 (3H, m), 7.27-7.20 (5H, m), 4.19-4.11 (1H, m), 3.62 (3H, s), 3.00-2.73 (2H, m), 1.33 (9H, s);  $m/z$  (ESI, 70V) 457 ( $M^+$ +Na).

**INTERMEDIATE 3****N'-(2,6-Difluorobenzoyl)-L-4-aminophenylalanine methyl ester hydrochloride**

A slurry of Intermediate 2 (6.93g) in 1M HCl/ethyl acetate (100ml) was stirred at room temperature for 3h. The solvent was removed *in vacuo*, ethyl acetate was added to the residue and the solid filtered off and dried to give the title compound as a white solid (6.0g).  $\delta_H$  (d<sup>6</sup> DMSO) 10.86 (1H, s), 8.73 (2H, br s), 7.65 (2H, d,  $\downarrow$  6.5Hz), 7.63-7.55 (1H, m), 7.26-7.21 (4H, m), 4.23 (1H, t,  $\downarrow$  6.6Hz), 3.70 (3H, s), 3.17-3.12 (2H, m);  $m/z$  (ESI, 70V) 335 ( $M^+$  +H).

**INTERMEDIATE 4****N-(Trimethylacetyl)-L-4-nitrophenylalanine methyl ester**

Trimethylacetyl chloride (17.75ml, 1.1eq) was added dropwise over 15min to a solution of L-4-nitrophenylalanine methyl ester hydrochloride (30g, 131mmol) and NMM (31.7ml, 2.2eq) in DMF (300ml) at 0°. Dimethylaminopyridine (catalytic) was added and the reaction mixture

stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate (500ml). This solution was washed with aqueous NaHCO<sub>3</sub> (300ml), citric acid (10%, 2 x 300ml), aqueous NaHCO<sub>3</sub> (500ml) and brine (500ml), dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give the title compound as a brown oil (34.15g, 85%)  $\delta_H$  (CDCl<sub>3</sub>) 8.1 (2H, d,  $\downarrow$  9.0Hz), 7.26 (2H, d,  $\downarrow$  9.0Hz), 6.16 (1H, m), 4.8 (1H, q), 3.72 (3H, s), 3.3 (1H, m), 3.2 (1H, m), 1.13 (9H, s);  $m/z$  (ESI, 70V) 309 ( $M^+ + H$ ).

#### 10 INTERMEDIATE 5

##### *N*-(Trimethylacetyl)-L-4-aminophenylalanine methyl ester

Palladium on charcoal (10% Pd, 3.0g) was added to solution of Intermediate 4 (34.15g, 110mmol) in methanol (1000ml) (degassed and under N<sub>2</sub>). The mixture was stirred under a hydrogen atmosphere (balloon) at room temperature overnight. The catalyst was filtered off and the filtrate concentrated *in vacuo* to give the title compound (28.32g, 92%).  $\delta_H$  (d<sup>6</sup> DMSO) 7.5 (1H, d,  $\downarrow$  8.0Hz), 6.84 (2H, d,  $\downarrow$  8.0Hz), 6.45 (2H, d,  $\downarrow$  8.0Hz), 4.85 (2H, t), 4.29 (1H, m), 3.59 (3H, s), 2.8 (2H, m);  $m/z$  (ESI, 70V) 279 ( $M^+ + H$ ).

20

#### INTERMEDIATE 6

##### *N*-Boc-O-(3,5-dichloroisonicotinyl)-L-tyrosine methyl ester

A mixture of *N*-Boc-L-tyrosine methyl ester (11.95g, 40.57mmol), 3,5-dichloro-4-bromomethyl pyridine (see International Patent Application No. PCT/GB99/00589; 10.74g, 44.56mmol) and caesium carbonate (14.52g, 44.56mmol) in DMF (100ml) was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and aqueous NaHCO<sub>3</sub>. The organic layer was washed with citric acid (10% x 2), aqueous NaHCO<sub>3</sub> (x 2) and brine, dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give the title compound as a brown solid (18.0g, 98%).  $\delta_H$  (d<sup>6</sup> DMSO) 8.72 (2H, s), 7.25 (1H, d,  $\downarrow$  8.2Hz), 7.19 (2H, d,  $\downarrow$  8.5Hz), 6.97 (2H, d,  $\downarrow$  8.5Hz), 5.20 (2H, s), 4.13 (1H, m), 3.61 (3H, s), 2.95 (1H, dd,  $\downarrow$  13.7, 5.0Hz), 2.82 (1H, m), 1.32 (9H, s);  $m/z$  (ESI, 60V) 477 ( $M^+ + H$ ).

**INTERMEDIATE 7****O-(3,5-Dichloroisonicotinyl)-L-tyrosine methyl ester hydrochloride**

Hydrochloric acid (4M in ethyl acetate, 100ml) was added to a solution of Intermediate 6 (18g, 39.6mmol) in ethyl acetate (100ml). The mixture was stirred at room temperature for 90min. The solid formed was filtered off, washed with ethyl acetate and dried to give the title compound as a light brown solid (14.6g).  $\delta_H$  ( $d^6$  DMSO) 8.79-8.60 (3H, including 2H, s), 7.20 (2H, d,  $\downarrow$  8.6Hz), 7.00 (2H, d,  $\downarrow$  8.6Hz), 7.3-6.9 (2H, v br), 5.21 (2H, s), 4.34-4.20 (1H, m), 3.67 (3H, s), 3.22-3.05 (2H, m);  $m/z$  (ESI, 60V) 355 ( $M^+ + H$ ).

**EXAMPLE 1****N-Isopropaloyl-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester**

Intermediate 1, hydrochloride salt (1.24mmol) in DMF (10ml) was treated successively with NMM (1.1 equivalents, 1.37mmol), isopropaloyl chloride (1.1 equivalents, 1.37mmol) and a catalytic amount of 4-dimethylaminopyridine. The reaction was stirred at 20° for 16h and evaporated to dryness. The residue was partitioned between 50% sodium hydrogen carbonate and ethyl acetate and the organics washed with 10% citric acid, brine and dried ( $MgSO_4$ ). Evaporation gave the title compound as a white solid. Yield 50%.  $^1H$ NMR [ $(CD_3)_2SO$ ]  $\delta_H$  10.85 (1H, s), 8.78 (2H, s), 8.15 (1H, d,  $\downarrow$  8.0Hz), 7.55 (2H, d,  $\downarrow$  8.5Hz), 7.22 (2H, d,  $\downarrow$  8.5Hz), 4.45 (1H, m), 3.62 (3H, s), 3.01 (1H, dd,  $\downarrow$  13.8, 5.4Hz), 2.88 (1H, dd,  $\downarrow$  13.8, 9.4Hz), 2.39 (1H, quint,  $\downarrow$  6.8Hz), 0.96 (3H, d,  $\downarrow$  6.8Hz) and 0.90 (3H, d,  $\downarrow$  6.8Hz).  $m/z$  (ES+ 60V) 462, 460 ( $MNa^+$ , 12, 22%), 440, 438 ( $MH^+$ , 71, 100%).

The following compounds of Examples 2 - 4 were prepared in a similar manner:

**EXAMPLE 2****N-Cyclopropaloyl-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester**

from Intermediate 1, hydrochloride salt and cyclopropanecarbonyl chloride. Yield 45%.  $^1H$ NMR [ $(CD_3)_2SO$ ]  $\delta_H$  10.87 (1H, s), 8.79 (2H, s), 8.51 (1H, d,  $\downarrow$  7.8Hz), 7.57 (2H, d,  $\downarrow$  8.5Hz), 7.23 (2H, d,  $\downarrow$  8.5Hz), 4.48 (1H, m), 3.62

(3H, s), 3.00 (1H, dd,  $\downarrow$  13.8, 5.7Hz), 2.89 (1H, dd,  $\downarrow$  13.8, 8.9Hz), 1.62 (1H, m) and 0.63 (4H, m). m/z (ES+ 60V) 460, 458 (MNa<sup>+</sup>, 15, 25%), 438, 436 (MH<sup>+</sup>, 63, 100%).

5 **EXAMPLE 3**

**N-Pivaloyl-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester**

from Intermediate 1, hydrochloride salt and pivaloyl chloride. Yield 44%.

<sup>1</sup>HNMR [(CD<sub>3</sub>)<sub>2</sub>SO]  $\delta$ H 10.8 (1H, s), 8.79 (2H, s), 7.71 (1H, d,  $\downarrow$  8.0Hz),  
10 7.55 (2H, d,  $\downarrow$  8.2Hz), 7.23 (2H, d,  $\downarrow$  8.5Hz), 4.44 (1H, m), 3.63 (3H, s),  
3.06 (1H, dd,  $\downarrow$  13.6, 5.4Hz), 2.97 (1H, dd,  $\downarrow$  13.6, 9.6Hz) and 1.04 (9H, s).  
m/z (ES+ 160V) 476, 474 (MNa<sup>+</sup>, 6, 10%), 454, 452 (MH<sup>+</sup>, 60, 100%).

**EXAMPLE 4**

15 **N-(<sup>n</sup>Propanoyl)-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester**

Prepared from Intermediate 1, hydrochloride salt and valeryl chloride as a white solid.  $\delta$ H (d<sup>6</sup> DMSO) 10.85 (1H, s), 8.79 (2H, s), 8.20 (1H, d,  $\downarrow$  8.0Hz), 7.55 (2H, d,  $\downarrow$  8.5Hz), 7.22 (2H, d,  $\downarrow$  8.5Hz), 4.49 (1H, m), 3.62  
20 (3H, s), 3.02 (1H, dd,  $\downarrow$  13.7, 5.3Hz), 2.85 (1H, dd,  $\downarrow$  13.7, 9.6Hz), 2.06 (2H, t,  $\downarrow$  7.3Hz), 1.38 (2H, m), 1.14 (2H, m), 0.80 (3H, t,  $\downarrow$  7.2Hz); m/z (ESI, 160V) 452 (M<sup>+</sup>+H).

**EXAMPLE 5**

25 **N-Isopropaloyl-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine.**

A solution of the compound of Example 1 (0.5mmol) in tetrahydrofuran (8ml) and water (6ml) was treated with lithium hydroxide dihydrate (1.5 equivalents, 0.75mmol) and stirred for 4h at 20°. The reaction was  
30 adjusted to pH2 with 2M hydrochloric acid and evaporated to dryness. Trituration of the residue with water gave the title compound as a white solid. Yield 90%. m.p. 257-258°. <sup>1</sup>HNMR [(CD<sub>3</sub>)<sub>2</sub>SO]  $\delta$ H 8.79 (2H, s), 8.00 (1H, d,  $\downarrow$  8.1Hz), 7.55 (2H, d,  $\downarrow$  8.5Hz), 7.23 (2H, d,  $\downarrow$  8.5Hz), 4.40 (1H, m), 3.03 (1H, dd,  $\downarrow$  13.7, 4.9Hz), 2.86 (1H, dd,  $\downarrow$  13.7, 9.4Hz), 2.39  
35 (1H, quint,  $\downarrow$  6.8Hz), 0.95 (3H, d,  $\downarrow$  6.8Hz) and 0.89 (3H, d,  $\downarrow$  6.8Hz). m/z (ES+, 60V) 448, 446 (MNa<sup>+</sup>, 9, 13%), 426, 424 (MH<sup>+</sup>, 66, 100%).

The following compounds of Examples 5 - 8 were prepared in a similar manner:

5 **EXAMPLE 6**

**N-Cyclopropaloyl-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine**

from the compound of Example 2. Yield 78%. m.p. 248-250°. <sup>1</sup>HNMR [(CD<sub>3</sub>)<sub>2</sub>SO] δH 8.79 (2H, s), 8.36 (1H, d, J 8.1Hz), 7.56 (2H, d, J 8.5Hz),  
10 7.24 (2H, d, J 8.5Hz), 4.43 (1H, m), 3.02 (1H, dd, J 13.8, 5.2Hz) 2.86 (1H, dd, J 13.8, 9.1Hz) and 1.63 (1H, m). m/z (ES+, 60V), 446, 444 (MNa<sup>+</sup>, 13, 24%), 424, 422 (MH<sup>+</sup>, 66, 100%).

**EXAMPLE 7**

15 **N-Pivaloyl-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine**

from the compound of Example 3. Yield 88%. m.p. 125-128°. <sup>1</sup>HNMR [(CD<sub>3</sub>)<sub>2</sub>SO] δH 10.83 (1H, s), 8.78 (2H, s), 7.53 (3H, m), 7.23 (2H, d, J 8.5Hz), 4.40 (1H, m), 3.06 (1H, dd, J 13.7, 4.7Hz), 2.96 (1H, dd, J 13.6, 9.8Hz) and 1.03 (9H, s). m/z (ES+, 160V) 462, 460 (MNa<sup>+</sup>, 16, 25%), 440,  
20 438 (MH<sup>+</sup>, 65, 100%).

**EXAMPLE 8**

**N-(n-Propanoyl)-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine**

25 from the compound of Example 4 as a white solid, m.p. 242-244°. δH (d<sup>6</sup> DMSO) 12.62 (1H, br s), 10.85 (1H, s), 8.78 (2H, s), 8.06 (1H, d, J 8.2Hz), 7.56 (2H, d, J 8.5Hz), 7.23 (2H, d, J 8.5Hz), 4.43 (1H, m), 3.04 (1H, dd, J 13.7, 4.8Hz), 2.82 (1H, dd, J 9.8Hz), 2.05 (2H, t, J 7.2Hz), 1.38 (2H, m), 1.14 (2H, m), 0.80 (3H, t, J 7.2Hz); m/z (ESI, 60V) 438 (M<sup>+</sup>+H).

30

**EXAMPLE 9**

**N-Acetyl-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester**

A mixture of Intermediate 1, hydrochloride salt (1.24mmol), HOBt (1.1  
35 equivalents, 1.36mmol), NMM (2.2 equivalents, 0.3ml) and glacial acetic acid (1.05 equivalents, 74μl) were stirred together in DMF(10ml) during the

addition of EDC (1.1 equivalents, 1.36mmol) and then for 16h at 20°. The reaction was evaporated and partitioned between ethyl acetate and sodium hydrogen carbonate. The organic phase was washed successively with 10% citric acid (x 2), sodium hydrogen carbonate (x 1) and brine (x 1) and dried (MgSO<sub>4</sub>). Evaporation gave the title compound as a pale lemon foam in 94% yield. <sup>1</sup>HNMR [(CD<sub>3</sub>)<sub>2</sub>SO] δH 10.01 (1H, s), 8.47 (2H, s), 7.54 (2H, d, J 8.5Hz), 7.01 (2H, d, J 8.5Hz), 6.47 (1H, d, J 7.9Hz), 4.75 (1H, m), 3.64 (3H, s), 2.99 (2H, m) and 1.90 (3H, s). m/z (ES+, 160V) 434, 432 (MNa<sup>+</sup>, 38, 54%), 410 (MH<sup>+</sup>, 69, 100%).

The following compound of Example 10 was prepared in a similar manner:

#### **EXAMPLE 10**

##### **N-(1-Phenyl-1-cyclopentanecarbonyl)-N'-(2,6-dichlorobenzoyl)-L-4-aminophenylalanine methyl ester**

from N'-(2,6-dichlorobenzoyl)-L-4-aminophenylalanine methyl ester hydrochloride and 1-phenyl-1-cyclopentanecarboxylic acid. δ<sub>H</sub> (d<sup>6</sup> DMSO) 7.7-7.4 (6H, m), 7.32-6.92 (8H, m), 4.45 (1H, m), 3.55 (3H, s), 3.1-2.85 (2H, m), 2.6, 2.3 (4H, m), 1.9-1.6 (4H, m), m/z (ESI 60V) 539 (M<sup>+</sup>+H).

#### **EXAMPLE 11**

##### **N-Acetyl-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine**

A solution of the compound of Example 9 (1.1mmol) in tetrahydrofuran (15ml) and water (12ml) was treated with lithium hydroxide (1.5 equivalents, 1.65mmol) and stirred for 16h at 20°. The reaction was adjusted to pH2 with 2M hydrochloric acid and evaporated down to a yellow oil. Trituration with water gave the title compound as an off-white solid in 65% yield. m.p. 198-202°. <sup>1</sup>HNMR [(CD<sub>3</sub>)<sub>2</sub>SO] δH 10.85 (1H, s), 8.78 (2H, s), 8.15 (1H, d, J 8.0Hz), 7.55 (2H, d, J 8.5Hz), 7.22 (2H, d, J 8.5Hz), 4.39 (1H, m), 3.00 (1H, dd, J 13.8, 5.0Hz) and 2.82 (1H, dd, J 13.8, 9.3Hz). m/z (ES+, 160V), 420, 418 (MNa<sup>+</sup>, 6,9%), 398, 396 (MH<sup>+</sup>, 47, 100%).

The following compound of Example 12 was prepared in a similar manner:

**EXAMPLE 12****N-(1-Phenyl-1-cyclopentanecarbonyl)-N'-(2,6-dichlorobenzoyl)-L-4-aminophenylalanine**

from the compound of Example 10.  $\delta_H$  ( $d_6$  DMSO) 10.60 (1H, s), 7.59-7.16 (10H, m), 6.98 (2H, d,  $J$  8.4Hz), 4.40 (1H, m), 3.30-2.7 (2H, m), 2.6-2.4 (4H, m), 1.9-1.5 (4H, m).  $m/z$ : (ESI, 60V) 525 ( $M^+ + H$ ).

**EXAMPLE 13****N-(Trimethylacetyl)-N'-(2,6-difluorobenzoyl)-L-4-aminophenylalanine methyl ester**

Trimethylacetyl chloride (443 $\mu$ l, 3.6mmol) was added to a solution of Intermediate x 23 (1.11g, 3mmol) and NMM (395 $\mu$ l, 3.6mmol) in DMF (20ml) at 0°. The reaction mixture was stirred at room temperature for 2h then poured into 1M hydrochloric acid. This mixture was extracted with ethyl acetate (2 x 50ml) and the combined extracts washed with aqueous NaHCO<sub>3</sub> (2 x 100ml) and brine (100ml), dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give the title compound as a white solid (740mg, 52%).  $\delta_H$  ( $d_6$  DMSO) 10.69 (1H, s), 7.68 (1H, d,  $J$  8.0Hz), 7.67-7.53 (3H, m), 7.26-7.19 (4H, m), 4.46-4.39 (1H, m), 3.62 (3H, s), 3.08-2.88 (2H, m), 1.03 (9H, s);  $m/z$  (ESI, 70V) 419 ( $M^+ + H$ ).

**EXAMPLE 14****N-(Trimethylacetyl)-N'-(2,6-difluorobenzoyl)-L-4-aminophenylalanine**

Prepared as a white solid. from the compound of Example 13 by ester hydrolysis in a similar manner to the compound of Example 5. m.p. 212-2.18°.  $\delta_H$  ( $d_6$  DMSO) 12.58 (1H, br s), 10.69 (1H, s), 7.62-7.48 (4H, m), 7.26-7.19 (4H, m), 4.43-4.35 (1H, m), 3.09-2.91 (2H, m), 1.03 (9H, s);  $m/z$  (ESI, 70V) 405 ( $M^+ + H$ ).

**EXAMPLE 15****N-Trimethylacetyl-N'-(2-chloronicotinoyl)-L-4-aminophenylalanine methyl ester**

Thionyl chloride (2.48ml, 10eq) and DMF (2 drops) were added to a solution of 2-chloronicotinic acid (535mg, 3.4mmol) in dichloromethane (3ml). The mixture was heated at reflux overnight then concentrated *in vacuo* and azeotroped with toluene (2 x 5ml) to give 2-chloronicotinoyl

chloride as a yellow oil. A solution of this acid chloride in dichloromethane (5ml) was added dropwise to a solution of Intermediate 5 (750mg, 2.69mmol) and NMM (355 $\mu$ l, 1.2eq) in dichloromethane (15ml) at 0°. Dimethylaminopyridine (catalytic) was added and the mixture stirred at room temperature for 2h. The mixture was then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (50ml) and washed with aqueous NaHCO<sub>3</sub> (2 x 50ml). The organic phase was dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give the title compound.  $\delta_H$  (CDCl<sub>3</sub>) 10.55 (1H, s), 8.51 (1H, m), 8.05 (1H, m), 7.67 (1H, m), 7.57 (3H, m), 7.2 (2H, m), 4.24 (1H, m), 3.62 (3H, s), 3.08 (2H, m), 1.03 (9H, s);  $m/z$  (ESI, 70V) 418 ( $M^+ + H$ ).

#### EXAMPLE 16

##### *N*-(Trimethylacetyl)-*N'*-(2-chloronicotinoyl)-*L*-4-aminophenylalanine

Prepared from the compound of Example 15 by ester hydrolysis using a similar method to the compound of Example 5.  $\delta_H$  (CDCl<sub>3</sub>) 12.7 (1H, br s), 10.58 (1H, s), 8.52 (1H, m), 8.06 (1H, m), 7.57 (4H, m), 7.21 (2H, m), 4.4 (1H, m), 3.02 (2H, m), 1.03 (9H, s);  $m/z$  (ESI, 70V) 404 ( $M^+ + H$ ).

#### EXAMPLE 17

##### *N*-(Trimethylacetyl)-*N'*-(2-chloroisonicotinoyl)-*L*-4-aminophenylalanine methyl ester

Carbon tetrachloride (1.32ml, 4eq) was added to a solution of 2-chloroisonicotinic acid (535mg, 3.4mmol) and triphenylphosphine (1.07g, 1.2eq) in tetrahydrofuran (30ml) and the mixture stirred overnight. A solution of Intermediate 5 (1.13g, 1.2eq) in tetrahydrofuran (15ml) was then added to this crude acid chloride at 0°. NMM (355 $\mu$ l, 1.2eq) was added and the mixture stirred overnight. The solvents were removed *in vacuo* and the residue dissolved in ethyl acetate (50ml), washed with hydrochloric acid (2M, 2 x 10ml), aqueous NaHCO<sub>3</sub> (2 x 100ml), water and brine (200ml). The organic phase was dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. Column chromatography (SiO<sub>2</sub>; ether/hexane, 9:1) gave the title compound as a white solid (290mg, 20%)  $\delta_H$  (CDCl<sub>3</sub>) 10.5 (1H, s), 9.6 (1H, d,  $\downarrow$  5.0Hz), 7.9 (1H, s), 7.7 (1H, m), 7.6 (3H, m), 7.2 (2H, d,  $\downarrow$  8.0Hz), 4.5 (1H, m), 3.63 (3H, s), 3.07 (2H, m), 1.05 (9H, s);  $m/z$  (ESI, 70V) 418 ( $M^+ + H$ ).



**EXAMPLE 18****N-(Trimethylactyl)-N'-(2-chloroisonicotinoyl)-L-4-aminophenylalanine**

Prepared from the compound of Example 17 by ester hydrolysis using a similar method to the compound of Example 5.  $\delta_H$  (CDCl<sub>3</sub>) 12.6 (1H, br s CO<sub>1</sub>H), 10.5 (1H, s, NH), 8.6 (1H, d); 8.05 (1H, s), 7.9 (1H, m), 7.7 (2H, m), 7.5 (1H, d), 7.3 (2H) 4.45 (1H, m), 3.05 (1H, m), 2.95 (1H, m), 1.2 (9H, s);  $m/z$  (ES<sup>+</sup>+ 70V); 4.04 ( $M^+$ -H).

**EXAMPLE 19**

10 **N-(Trimethylacetyl)-O-(3,5-dichloroisonicotinoyl)-L-tyrosine methyl ester**

Trimethylacetyl chloride (406 $\mu$ l, 3.3mmol) was added to a solution of Intermediate 7 (1.17g, 3mmol) and NMM (725 $\mu$ l, 6.6mmol) in dichloromethane (50ml). The mixture was stirred at room temperature for 15 3 days. Dichloromethane and citric acid (10%) were added, the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with aqueous NaHCO<sub>3</sub> (x 2) and brine, dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give the title compound (1.12g, 86%).  $\delta_H$  (d<sup>6</sup> DMSO) 8.71 (2H, s), 7.66 (1H, d,  $\downarrow$  8.0Hz), 7.16 (2H, d,  $\downarrow$  8.6Hz), 6.94 (2H, d,  $\downarrow$  8.6Hz), 5.19 (2H, s), 4.45-4.37 (1H, m), 3.61 (3H, s), 3.05-2.89 (2H, m), 1.01 (9H, s);  $m/z$  (ESI, 60V) 439 ( $M^+$ +H).

**EXAMPLE 20****N-(Trimethylacetyl)-O-(3,5-dichloroisonicotinyl)-L-tyrosine**

25 Prepared from the compound of Example 19 by ester hydrolysis using a similar method to the compound of Example 5 to yield a white solid.  $\delta_H$  (d<sup>6</sup> DMSO) 8.70 (2H, s), 7.45 (1H, d,  $\downarrow$  8.6Hz), 7.16 (2H, d,  $\downarrow$  8.6Hz), 6.94 (2H, d,  $\downarrow$  8.6Hz), 5.18 (2H, s), 4.39-4.34 (1H, m), 3.03 (1H, dd,  $\downarrow$  13.7, 4.6Hz), 2.91 (1H, dd,  $\downarrow$  13.7, 9.9Hz), 1.00 (9H, s);  $m/z$  (ESI, 60V) 325 ( $M^+$ +H).

**EXAMPLE 21****N-(<sup>n</sup>Butylsulphonyl)-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester**

35 <sup>n</sup>Butanesulphonyl chloride (0.17ml, 1.3mmol) was added to a solution of Intermediate 1 (500mg, 1.24mmol) and diisopropylethylamine (0.7ml,

3.9mmol) in dichloromethane (10ml). The reaction mixture was stirred for 16h at room temperature, then washed with citric acid (10%), aqueous NaHCO<sub>3</sub> and brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. Column chromatography (SiO<sub>2</sub>; ethyl acetate/hexane, 3:1) gave the title compound (120mg).  $\delta_H$  (d<sup>6</sup> DMSO) 10.88 (1H, s), 8.79 (2H, s), 7.80 (1H, d,  $\downarrow$  8.9Hz), 7.59 (2H, d,  $\downarrow$  8.3Hz), 7.30 (2H, d,  $\downarrow$  8.3Hz), 4.10 (1H, m), 3.67 (3H, s), 3.02 (1H, dd,  $\downarrow$  13.7, 4.8Hz), 2.77 (1H, dd,  $\downarrow$  13.6, 10.1Hz), 2.60 (2H, t,  $\downarrow$  8.3Hz), 1.22 (4H, m), 0.76 (3H, t,  $\downarrow$  7.2Hz);  $m/z$  (ESI, 60V) 488 ( $M^+ + H$ ).

#### 10 **EXAMPLE 22**

##### **N-(<sup>n</sup>Butylsulphonyl)-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine**

Prepared from the compound of Example 21 by ester hydrolysis using a similar method to the compound of Example 5 to yield a white solid. m.p. 252-254°.  $\delta_H$  (d<sup>6</sup> DMSO) 12.86 (1H, br s), 10.87 (1H, s), 8.79 (2H, s), 7.59 (3H, m + d  $\downarrow$  4.4Hz), 7.30 (2H, d,  $\downarrow$  8.4Hz), 3.98 (1H, m), 3.04 (1H, dd,  $\downarrow$  13.6, 4.7Hz), 2.75 (1H, dd,  $\downarrow$  13.6, 10.2Hz), 2.56 (2H, m), 1.20 (4H, m), 0.76 (3H, t,  $\downarrow$  7.2Hz);  $m/z$  (ESI, 60V) 474 ( $M^+ + H$ ).

#### 20 **EXAMPLE 23**

##### **N-( $\alpha$ -Sulphonyltoluene)-O-(2,6-dichlorobenzyl)-L-tyrosine methyl ester**

To O-2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride (0.5gm, 1.3mmol) in ethyl acetate (10ml), was added saturated sodium bicarbonate solution (5ml). The mixture was stirred for 15 min before isolating the organic layer and extracting the aqueous layer with ethyl acetate (3 x 3ml). The combined organic solutions were washed with brine (2 x 5ml), dried (MgSO<sub>4</sub>), and the solvent evaporated *in vacuo*. The residue was dissolved in anhydrous pyridine (3ml) and cooled in an ice/water bath before the dropwise addition of  $\alpha$ -toluene sulphonyl chloride (243mg, 1.3mmol). After complete addition the cooling bath was removed and the solution stirred at room temperature for 16h, before pouring onto water (30ml) and extracting the product with ethyl acetate (2 x 20ml). The combined extracts were washed with water (3 x 10ml), dried (MgSO<sub>4</sub>), and solvent removed *in vacuo*. Column chromatography (SiO<sub>2</sub>, ethyl acetate/hexane, 1:1) gave the title compound as a viscous yellow oil.  $\delta_H$  (CD<sub>3</sub>OD) 7.36-7.20 (4H, m), 7.00 (2H, d,  $\downarrow$  8.8Hz), 6.90 (2H, d,  $\downarrow$  8.8Hz),

4.74 (1H, d,  $\downarrow$  8.9Hz), 4.1 (3H, m), 3.72 (3H, s), 2.94 (2H, d,  $\downarrow$  5.9Hz);  $m/z$  (ESI, 60V) 525 ( $\text{NH}_4$  adduct).

#### **EXAMPLE 24**

##### **5 N-( $\alpha$ -Sulphonyltoluene)-O-(2,6-dichlorobenzyl)-L-tyrosine**

To the compound of Example 23 (220mg, 0.43mmol) dissolved in water (5ml) and tetrahydrofuran (10ml) was added lithium hydroxide monohydrate (27mg, 1.5equiv). The resulting solution was stirred at room temperature for 2h. The organic solvent was removed *in vacuo* and the residue dissolved in water. This solution was acidified with dilute hydrochloric acid and the product extracted into ethyl acetate (3 x 5ml), the combined extracts were washed with water (2 x 4ml), dried ( $\text{Mg}_2\text{SO}_4$ ), and the solvent removed to yield the title compound as a white powder.  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 7.35-7.21 (8H, m), 7.1 (2H, d,  $\downarrow$  7.7Hz), 6.9 (2H, d,  $\downarrow$  7.7Hz), 4.6 (1H, d,  $\downarrow$  8.9Hz), 4.1 (3H, m), 3.0 (2H, m).  $m/z$  (ESI 60V) 511 ( $\text{NH}_4$  adduct).

#### **EXAMPLE 25**

##### **N-( $\alpha$ -Propanesulphonyl)-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester**

20 The title compound was prepared as a white solid from Intermediate 1 and propanesulphonyl chloride in a similar manner to the compound of Example 21.  $\delta_{\text{H}}$  ( $\text{d}^6$  DMSO) 10.87 (1H, s), 8.78 (2H, s), 7.81 (1H, d,  $\downarrow$  9.0Hz), 7.59 (2H, d,  $\downarrow$  8.4Hz), 7.29 (2H, d,  $\downarrow$  8.4Hz), 4.09 (1H, br m), 3.67 (3H, s), 3.04 (1H, dd,  $\downarrow$  13.7, 5.3Hz), 2.78 (1H, dd,  $\downarrow$  13.7, 9.8Hz), 2.59 (2H, m), 1.42-1.30 (2H, br m) and 0.76 (3H, t,  $\downarrow$  7.3Hz);  $m/z$  (ESI, 60V) 474 ( $\text{M}^+ + \text{H}$ ).

#### **EXAMPLE 26**

##### **N-( $\alpha$ -Propanesulphonyl)-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine**

30 Prepared from the compound of Example 25 by ester hydrolysis in a similar manner to the compound of Example 25 to yield a white solid.  $\delta_{\text{H}}$  ( $\text{d}^6$  DMSO) 10.86 (1H, s), 8.78 (2H, s), 7.58 (2H, d,  $\downarrow$  8.3Hz), 7.30 (2H, d,  $\downarrow$  8.3Hz), 3.98 (1H, m), 3.03 (1H, dd,  $\downarrow$  13.6, 6.9Hz), 2.76 (1H, dd,  $\downarrow$  13.6, 9.1Hz), 2.58 (2H, m), 1.44-1.32 (2H, m) and 0.76 (3H, t,  $\downarrow$  7.4Hz);  $m/z$  (ESI, 60V), 460 ( $\text{M}^+ + \text{H}$ ).

**EXAMPLE 27****N-(Benzyloxycarbonyl)-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester**

- 5 Benzyl chloroformate (0.32ml, 2.22mmol) was added to a solution of Intermediate 1 (750mg, 1.85mmol) diisopropylethylamine (0.81ml, 4.64mmol) and dimethylaminopyridine (catalytic) in dichloromethane (20ml) at 0°. The reaction mixture was stirred for 48h at room temperature, then washed with citric acid (10%), aqueous NaHCO<sub>3</sub> and
- 10 brine, dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to give an oil solid. Trituration (ethyl acetate/hexane, 1:1) gave the title compound as a white solid (225mg).  $\delta_H$  (d<sup>6</sup> DMSO) 10.88 (1H, s), 8.80 (2H, s), 7.82 (1H, d,  $\downarrow$  8.2Hz), 7.57 (2H, d,  $\downarrow$  8.5Hz), 7.32 (7H, m), 4.98 (2H, s), 4.28 (1H, m), 3.65 (3H, s), 3.05 (1H, dd,  $\downarrow$  13.7, 4.9Hz), 2.85 (1H, dd,  $\downarrow$  13.7, 10.3Hz);
- 15  $m/z$  (ESI, 60V) 502 ( $M^+ + H$ ).

**EXAMPLE 28****N-(Benzyloxycarbonyl)-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine**

- 20 Prepared from the compound of Example 27 by ester hydrolysis in a similar manner to the compound of Example 5.  $\delta_H$  (d<sup>6</sup> DMSO) 12.72 (1H, br s), 10.87 (1H, s), 8.80 (2H, s), 7.65 (1H, d,  $\downarrow$  8.5Hz), 7.57 (2H, d,  $\downarrow$  8.5Hz), 7.28 (7H, m), 4.19 (1H, m), 3.06 (1H, dd,  $\downarrow$  15.0, 5.5Hz), 2.82 (1H, dd,  $\downarrow$  15.0, 10.5Hz);  $m/z$  (ESI, 160V) 488 ( $M^+ + H$ ).

25

**EXAMPLE 29****N-(Ethoxycarbonyl)-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester**

- Prepared as an off-white solid from Intermediate 1 and ethyl chloroformate
- 30 in a similar manner to the compound of Example 27.  $\delta_H$  (CDCl<sub>3</sub>) 8.56 (2H, s), 7.63 (1H, br s), 7.54 (2H, d,  $\downarrow$  8.5Hz), 7.16 (2H, m), 5.16 (1H, br s), 4.64 (1H, m), 4.10 (2H, q,  $\downarrow$  7.1Hz), 3.75 (3H, s), 3.11 (2H, m), 1.23 (3H, t,  $\downarrow$  7.1Hz);  $m/z$  (ESI, 60V) 440 ( $M^+ + H$ ).

**EXAMPLE 30****N-(Ethoxycarbonyl)-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine**

Prepared as a white solid from the compound of Example 30 by ester hydrolysis in a similar manner to the compound of Example 5.  $\delta_H$  ( $d^6$  DMSO) 10.86 (1H, s), 8.79 (2H, d,  $\downarrow$  0.74Hz), 7.56 (2H, d,  $\downarrow$  8.4Hz), 7.41 (1H, d,  $\downarrow$  8.4Hz), 7.26 (2H, d,  $\downarrow$  8.4Hz), 4.13 (1H, m), 3.93 (2H, m), 3.03 (1H, dd,  $\downarrow$  13.7, 4.5Hz), 2.80 (1H, dd,  $\downarrow$  13.6, 10.6Hz), 1.12 (3H, t,  $\downarrow$  7.1Hz);  $m/z$  (ESI, 60V) 426 ( $M^+ + H$ ).

**EXAMPLE 31****N-(1-Adamantylcarbonyl)-N'-(2,6-dichlorobenzoyl)-L-4-aminophenylalanine methyl ester**

Prepared as a white solid from N'-(2,6-dichlorobenzoyl)-L-4-aminophenylalanine methyl ester hydrochloride and 1-adamantanecarbonyl chloride by a method similar to that of Example 1.  $\delta_H$  ( $CDCl_3$ ) 7.5 (2H, d,  $\downarrow$  8.5Hz), 7.5-7.3 (4H, m), 7.1 (2H, d,  $\downarrow$  8.5Hz), 6.1 (1H, broad d), 4.8 (1H, m), 3.7 (3H, s), 3.1 (2H, m), 2.0 (3H, broad s), 1.8 (6H, broad s), 1.7 (6H, broad s).  $m/z$  (ESI 60V) 529 ( $M^+ + H$ ).

**EXAMPLE 32****N-(1-Adamantylcarbonyl)-N'-(2,6-dichlorobenzoyl)-L-4-aminophenylalanine**

Prepared from the compound of Example 31 by ester hydrolysis in a similar manner to the compound of Example 5.  $\delta_H$  ( $d^6$  DMSO) 10.6 (1H, s), 7.7-7.3 (5H, m), 7.2 (2H, d,  $\downarrow$  8.2Hz), 4.5-4.3 (1H, m), 3.2-2.9 (2H, m), 2.0 (3H, broad s), 1.8-1.6 (12H, two broad s).  $m/z$  (ESI 60V) 515 ( $M^+ + H$ ).

The following compounds of Examples 33 and 34 were prepared by hydrolysis of the corresponding ester in a similar manner to the compound of Example 5:

**EXAMPLE 33****N-(2,6-Dichlorophenylacetoyl)-N'-(2,6-dichlorobenzoyl)-L-4-aminophenylalanine**

The ester starting material was prepared from *N'*-(2,6-dichlorobenzoyl)-*L*-4-aminophenylalanine methyl ester hydrochloride and 2,6-dichlorophenylacetyl chloride by a method similar to that of Example 1.  $\delta_{\text{H}}$  ( $\text{d}^6$  DMSO) 10.66 (1H, s, NH), 8.37 (1H, dd,  $\downarrow$  8.1Hz, NH), 7.60-7.20 (10H, m, Ar-H), 4.42 (1H, m,  $\alpha$ -CH), 3.79 (2H, m,  $\text{CH}_2\text{Ar}$ ), 3.05 (1H, dd,  $\downarrow$  13.7, 5.0Hz,  $\text{CHCH}_\text{A}\text{H}_\text{B}$ ), 2.98 (1H, m,  $\text{CHCH}_\text{A}\text{H}_\text{B}$ ).  $m/z$  (ESI, 60V) 538 ( $\text{MH}^+$ ).

#### EXAMPLE 34

##### 10 *N*-(Diphenylacetyl)-*N'*-(2,6-dichlorobenzoyl)-*L*-4-aminophenyl alanine

The ester starting material was prepared from *N'*-(2,6-dichlorobenzoyl)-*L*-4-aminophenylalanine methyl ester hydrochloride and diphenylacetyl chloride by a method similar to that of Example 1.  $\delta_{\text{H}}$  ( $\text{d}^6$  DMSO) 10.67 (1H, s, NH), 8.55 (1H, d,  $\downarrow$  8.2Hz, NH), 7.61-6.97 (17H, m, Ar-H), 5.01 (1H, s,  $\text{CHAr}_2$ ), 4.53 (1H, m,  $\alpha$ -CH), 3.05 (1H, m,  $\text{CHCH}_\text{A}\text{H}_\text{B}$ ), 2.84 (1H, m,  $\text{CHCH}_\text{A}\text{H}_\text{B}$ ).  $m/z$  (ESI, 60V), 547 ( $\text{MH}^+$ ).

#### EXAMPLE 35

##### 20 *N*-(Ethylaminocarbonyl)-*N'*-(3,5-dichloroisonicotinoyl)-*L*-4-aminophenylalanine methyl ester

A solution of Intermediate 1 hydrochloride (0.39g, 1mmol) and NMM (0.13ml, 1.2mmol) in tetrahydrofuran (10ml) was treated with ethyl isocyanate (0.079ml, 1.1mmol) and the reaction stirred overnight at room temperature. The mixture was partitioned between dichloromethane (20ml) and water (20ml), the aqueous layer extracted with dichloromethane (20ml) and the combined organic layers dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to give the title compound as a white solid, 0.29, 66% which was used without further purification.

30

#### EXAMPLE 36

##### 35 *N*-(Ethylaminocarbonyl)-*N'*-(3,5-dichloroisonicotinoyl)-*L*-4-aminophenylalanine

A solution of the compound of Example 35 (0.29g, 0.66mmol) in tetrahydrofuran (5ml) and water (5ml) was treated with  $\text{LiOH}\cdot\text{H}_2\text{O}$  (42mg, 1.0mmol) and stirred overnight at room temperature. The reaction mixture

was acidified to pH 1 with 10% hydrochloric acid and the resulting white solid isolated by filtration, washed with water (2 x 10ml) and dried *in vacuo* to give the title compound 0.22g, 78%.  $\delta_H$  ( $d^6$  DMSO) 10.87 (1H, s, NH), 8.79 (2H, s, pyr-H), 7.97 (2H, d,  $\downarrow$  8.5Hz, Ar-H), 7.19 (2H, d,  $\downarrow$  8.5Hz, Ar-H), 6.04 (1H, m, NH<sub>4</sub>Et), 5.97 (1H, d,  $\downarrow$  8.4Hz, CHNH), 4.34 (1H, m,  $\alpha$ -CH), 3.02-2.94 (3H, m, CHCH<sub>2</sub>AB + CH<sub>2</sub>CH<sub>3</sub>), 2.85 (1H, dd,  $\downarrow$  13.8, 7.6Hz, CHCH<sub>2</sub>AB), 0.96 (3H, t,  $\downarrow$  7.2Hz, CH<sub>2</sub>CH<sub>3</sub>).  $m/z$  (ESI, 70V) 425 (MH<sup>+</sup>).

- 10 The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these assays an IC<sub>50</sub> value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

**$\alpha_4\beta_1$  Integrin-dependent Jurkat cell adhesion to VCAM-Ig**

- 96 well NUNC plates were coated with F(ab)<sub>2</sub> fragment goat anti-human IgG Fc $\gamma$ -specific antibody [Jackson Immuno Research 109-006-098: 100  $\mu$ l at 2  $\mu$ g/ml in 0.1M NaHCO<sub>3</sub>, pH 8.4], overnight at 4°. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing (3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then performed at 37° for 30 min in a total volume of 200  $\mu$ l containing 2.5 x 10<sup>5</sup> Jurkat cells in the presence or absence of titrated test compounds.
- 30 Each plate was washed (2x) with medium and the adherent cells were fixed with 100 $\mu$ l methanol for 10 minutes followed by another wash. 100 $\mu$ l 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100 $\mu$ l 50% (v/v) ethanol in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

**$\alpha_4\beta_1$  Integrin-dependent JY cell adhesion to MAdCAM-Ig**

- This assay was performed in the same manner as the  $\alpha_4\beta_1$  assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-  
5 line of the  $\beta$ -lympho blastoid cell-line JY was used in place of Jurkat cells. The IC<sub>50</sub> value for each test compound was determined as described in the  $\alpha_4\beta_1$  integrin assay.

 **$\alpha_5\beta_1$  Integrin-dependent K562 cell adhesion to fibronectin**

- 10 96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5 $\mu$ g/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 100 $\mu$ l PBS/1% BSA at room temperature on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at  
15 37°C in a total volume of 200 $\mu$ l containing 2.5x 10<sup>5</sup> K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed and stained as described in the  $\alpha_4\beta_1$  assay above.

 **$\alpha_m\beta_2$ -dependent human polymorphonuclear neutrophils adhesion to plastic**

- 96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h at 37°C. 2 x 10<sup>5</sup> freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to the wells in a total volume of 200 $\mu$ l in  
25 the presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and 100 $\mu$ l 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well.  
30 The plates were then left on a rocker at room temperature for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H<sub>2</sub>O<sub>2</sub> (Sigma) and 50 $\mu$ g/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.



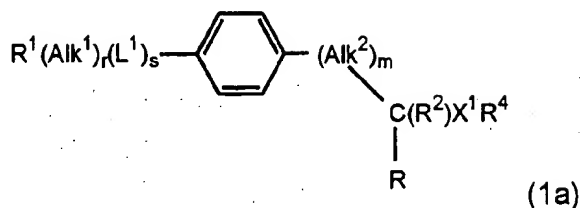
**$\alpha$ IIb/ $\beta$ <sub>3</sub>-dependent human platelet aggregation**

Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of  $6 \times 10^8$ /ml in autologous plasma. Cuvettes contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; MgCl<sub>2</sub>.H<sub>2</sub>O 0.427; CaCl<sub>2</sub> 0.2; KCl 0.2; D-glucose 1.0; NaHCO<sub>3</sub> 1.0; NaHPO<sub>4</sub>.2H<sub>2</sub>O 0.065). Aggregation was monitored following addition of 2.5 $\mu$ M ADP (Sigma) in the presence or absence of inhibitors.

In the above assays the compounds of the invention generally have IC<sub>50</sub> values in the  $\alpha$ <sub>4</sub> $\beta$ <sub>1</sub> and  $\alpha$ <sub>4</sub> $\beta$ <sub>7</sub> assays of 1  $\mu$ M and below. The compounds of the Examples typically had IC<sub>50</sub> values of 100nM and below in these assays and demonstrated selective inhibition of  $\alpha$ <sub>4</sub> $\beta$ <sub>1</sub>. In the other assays featuring  $\alpha$  integrins of other subgroups the same compounds had IC<sub>50</sub> values of 50 $\mu$ M and above thus demonstrating the potency and selectivity of their action against  $\alpha$ <sub>4</sub> integrins.

**CLAIMS**

1. A compound of formula (1a):



wherein

R is a carboxylic acid (-CO<sub>2</sub>H) or a derivative thereof;

R<sup>1</sup> is an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Alk<sup>1</sup> is an optionally substituted aliphatic or heteroaliphatic chain;

L<sup>1</sup> is a linker atom or group;

r and s, which may be the same or different, is each zero or an integer 1;

Alk<sup>2</sup> is a straight or branched alkylene chain;

m is zero or an integer 1;

R<sup>2</sup> is a hydrogen atom or a methyl group;

X<sup>1</sup> is a group selected from -N(R<sup>3</sup>)CO- (where R<sup>3</sup> is a hydrogen atom or a straight or branched alkyl group); -N(R<sup>3</sup>)SO<sub>2</sub>-, -N(R<sup>3</sup>)C(O)O- or -N(R<sup>3</sup>)CON(R<sup>3a</sup>)- (where R<sup>3a</sup> is a hydrogen atom or a straight or branched alkyl group);

R<sup>4</sup> is an optionally substituted aliphatic, cycloaliphatic or polycycloaliphatic group;

and the salts, solvates, hydrates and N-oxides thereof.

2. A compound according to Claim 1 wherein R is a carboxylic acid (-CO<sub>2</sub>H) group.

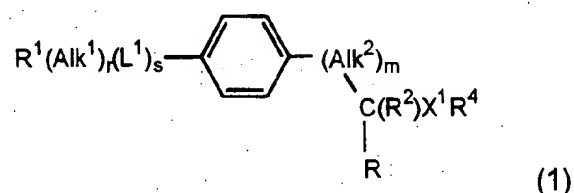
3. A compound according to Claim 1 or Claim 2 wherein R<sup>1</sup> is an optionally substituted aromatic or heteroaromatic group.

4. A compound according to Claim 3 wherein R<sup>1</sup> is an optionally substituted phenyl, pyridyl or pyrimidinyl group.
5. A compound according to any one of Claim 1 to Claim 4 wherein  
5 -(Alk<sup>1</sup>)<sub>r</sub>(L<sup>1</sup>)<sub>s</sub>- is a -CH<sub>2</sub>O- or -CON(R<sup>5</sup>)- group where R<sup>5</sup> is a hydrogen atom or a straight or branched alkyl group.
6. A compound according to Claim 5 wherein -(Alk<sup>1</sup>)<sub>r</sub>(L<sup>1</sup>)<sub>s</sub>- is a -CONH-  
10 group.
7. A compound according to any one of Claim 1 to Claim 6 wherein Alk<sup>2</sup>  
is -CH<sub>2</sub>-, m is an integer 1, and R<sup>2</sup> is a hydrogen atom.
8. A compound according to any one of Claim 1 to Claim 7 wherein X<sup>1</sup>  
15 is a -NHCO-, -NHSO<sub>2</sub>-, -NHC(O)O- or -NHCONH- group.
9. A compound according to Claim 8 wherein X<sup>1</sup> is a -NHCO- group.
10. A compound according to any one of the preceding claims wherein  
20 R<sup>4</sup> is an optionally substituted straight or branched C<sub>1-6</sub>alkyl group or an optionally substituted C<sub>3-7</sub>cycloalkyl or C<sub>7-10</sub>tricycloalkyl group.
11. A compound according to Claim 10 wherein R<sup>4</sup> is an optionally  
25 substituted straight or branched C<sub>1-4</sub>alkyl, cyclopropyl, cyclobutyl, cyclopentyl or adamantyl group.
12. A compound which is:  
N-Isopropaloyl-N-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine.;  
30 N-Cyclopropaloyl-N-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;  
N-Acetyl-N'-(3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;  
N-(Trimethylacetyl)-N'-(2,6-difluorobenzoyl)-L-4-aminophenylalanine;  
N-(1-Adamantylcarbonyl)-N'-(2,6-dichlorobenzoyl)-L-4-aminophenyl  
35 alanine;  
and the salts, solvates, hydrates and N-oxides thereof.

13. A pharmaceutical composition comprising a compound according to Claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

5

14. A compound of formula (1):



wherein

- 10 R is a carboxylic acid (CO<sub>2</sub>H) or a derivative thereof;  
 R<sup>1</sup> is a hydrogen atom or a hydroxyl, straight or branched alkoxy or optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;  
 15 Alk<sup>1</sup> is an optionally substituted aliphatic or heteroaliphatic chain;  
 L<sup>1</sup> is a linker atom or group;  
 r and s, which may be the same or different, is each zero or an integer 1 provided that when r is zero R<sup>1</sup> is an optionally substituted cycloaliphatic, polycycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;  
 20 Alk<sup>2</sup> is a straight or branched alkylene chain;  
 m is zero or an integer 1;  
 R<sup>2</sup> is a hydrogen atom or a methyl group;  
 X<sup>1</sup> is a group selected from -N(R<sup>3</sup>)CO- (where R<sup>3</sup> is a hydrogen atom or a straight or branched alkyl group); -N(R<sup>3</sup>)SO<sub>2</sub>-, -N(R<sup>3</sup>)C(O)O- or -N(R<sup>3</sup>)CON(R<sup>3a</sup>)- (where R<sup>3a</sup> is a hydrogen atom or a straight or branched alkyl group);  
 25 R<sup>4</sup> is an optionally substituted aliphatic, cycloaliphatic or polycycloaliphatic group;  
 30 and the salts, solvates, hydrates and N-oxides thereof, for use in modulating cell adhesion

# INTERNATIONAL SEARCH REPORT

Internat. Application No.

PCT/GB 99/01758

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C233/87 C07D213/81 A61K31/195 A61K31/455

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                  | Relevant to claim No. |
|------------|---|-----------------------|
| E          | WO 99 48879 A (CELLTECH THERAPEUTICS LIMITED) 30 September 1999 (1999-09-30)<br>the whole document. | 1,13,14               |
| E          | WO 99 43642 A (CELLTECH THERAPEUTICS) 2 September 1999 (1999-09-02)<br>the whole document           | 1,13,14               |
| P,X        | WO 99 10312 A (F. HOFFMANN-LA ROCHE AG) 4 March 1999 (1999-03-04)<br>the whole document             | 1,13,14               |
| E          | WO 99 37618 A (CELLTECH THERAPEUTICS LIMITED) 29 July 1999 (1999-07-29)<br>the whole document       | 1,13,14               |
|            | ---<br>-/--   |                       |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

12 November 1999

Date of mailing of the international search report

22/11/1999

Name and mailing address of the ISA

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Kyriakakou, G

# INTERNATIONAL SEARCH REPORT

Internat'l Application No  
PCT/GB 99/01758

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                      | Relevant to claim No. |
|------------|---|-----------------------|
| E          | WO 99 35163 A (CELLTECH THERAPEUTICS LIMITED) 15 July 1999 (1999-07-15)<br>the whole document<br>---    | 1, 13, 14             |
| P, A       | WO 98 54207 A (CELLTECH THERAPEUTICS LIMITED) 3 December 1998 (1998-12-03)<br>the whole document<br>--- | 1, 13, 14             |
| Y          | WO 98 00395 A (MERCK PATENT GMBH) 8 January 1998 (1998-01-08)<br>the whole document<br>---              | 1, 13, 14             |
| Y          | EP 0 710 657 A (MERCK PATENT GMBH) 8 May 1996 (1996-05-08)<br>the whole document<br>-----               | 1, 13, 14             |

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 01758

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-11(in part), 13(in part), 14(in Part),12

Present claims 1,2,3,4, 13,14relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear namely those compounds recited in the examples and closely related homologous compounds.

Moreover the expressions, "linker atom or group", " a derivatif thereof"( cf. the definitions of L1 and R in the present claim 1 is considered to be unclear in the sense of Article 6 PCT, since this term is non-limiting as regards the structure of the compound of formula (1).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat I Application No

PCT/GB 99/01758

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
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| WO 9948879 A                              | 30-09-1999          | NONE                       |                     |
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